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(54) Title: OPTICALLY PURE S(-) NADOLOL FOR TREATMENT OF CARDIOVASCULAR DISORDERS

(57) Abstract

Optically pure S(-) nadolol, which is substantially free of the R(+) enantiomer, is a potent beta-blocker for relieving the symptoms of angina pectoris and hypertension in individuals. A method is disclosed utilizing the optically pure S(-) enantiomer of nadolol for treating cardiovascular disorders while reducing undesirable side effects associated with the administration of the racemic drug.

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OPTICALLY PURE S(-) NADOLOL FOR TREATMENT OF CARDIOVASCULAR DISORDERS

Description

Background

Nadolol is a drug belonging to the general class of compounds known as beta-blockers. Beta-blockers are beta-selective adrenoreceptor blocking agents, and include well-known commercial products such as propanolol and atenolol.

Nadolol is a potent cardiac regulator with both antihypertensive and antianginal activity. The beta-adrenoreceptor blocking activity of nadolol is characterized by a reduction in resting and exercise heart rate and cardiac output, a reduction in the systolic and diastolic blood pressure at rest and on exercise, inhibition of isoproterenol-induced tachycardia and reduction in reflex orthostatic tachycardia. By blocking the positive chronotropic and inotropic effects of catecholamines and by decreasing blood pressure, nadolol generally reduces the oxygen requirements of the heart, at any given level of effort.

Nadolol is known to be a non-selective beta blocker. That is, it interacts strongly with both cardiac (beta-1 type) adrenoreceptors and with those adrenoreceptors in bronchial and vascular (beta-2 type) musculature. Because of the non-selectivity of nadolol, it is

contraindicated in patients with bronchial asthma and other obstructive airways diseases.

Nadolol is not metabolized to a significant degree by the liver. It is excreted by the kidneys unchanged. Because the drug has an appreciable half-life (about 20-24 hours) it can be administered on a once-daily dosage basis. However, because of its relatively long half-life and excretion characteristics, dosage of nadolol must be adjusted with care in patients with impaired renal function.

Nadolol has been found to possess substantially less direct myocardial depressant activity than some other beta-blockers. For instance, it was found to exhibit about 1/20th the myocardial depressant effect of propranolol in experiments with anesthetized dogs.

Nadolol is a racemic mixture. That is, it is a mixture of optical isomers, called enantiomers. Enantiomers are structurally similar compounds which differ only in that one isomer is a configurational mirror image of the other and the mirror images cannot be superimposed. This phenomenon is known as chirality. Most biological molecules exhibit chirality. Although structurally similar, enantiomers can have profoundly different effects in biological systems.

Few studies have been conducted to investigate biological characteristics of the enantiomers of nadolol. Raxworthy et al. (Xenobiotica 1986, Vol. 16, No. 1, pp. 47-52) set out to study substrate selectivity and stereoselectivity for catechol-O-methyl transferase, but found that nadolol was not a substrate for this liver

enzyme. Their finding seems consistent with the known low degree of metabolism of nadolol in the liver.

It is generally known that for other beta-blocking drugs, the physiological action is almost exclusively due to the S(-) enantiomers. (This topic has been reviewed by Abou-Gharbia et al. in Handbook of Stereoisomers: Therapeutic Drugs, D.F. Smith (ed.), CRC Press, 1989, pp. 65-124.) This observation, which has been made for propranolol and several other members of the class, has led to a generally-accepted view that it is true of all beta-blockers. However, it is not generally recognized that the co-administration of the R-enantiomer is associated with side effects of the drug.

Summary of the Invention

The present invention relates to a method of treating cardiovascular disorders, including angina pectoris and hypertension, in an individual comprising administering to the individual a beta-blocking or antihypertensive amount of the levorotatory or S(-) enantiomer of nadolol , which is substantially free of the dextrorotatory or R(+) enantiomer. The method is useful in treating cardiovascular disorders and in treating hypertension while reducing or avoiding undesirable side effects such as gastro-intestinal distress, dizziness, fatigue, as well as certain cardiovascular and central nervous system effects, and allergic reactions, which are due, at least in part, to the presence of the R(+) enantiomer. For beta-blocking drugs, it is important to have a beta-blocking and antihypertensive composition which also minimizes these

side effects. A composition containing the S(-) isomer of nadolol is particularly useful because the S(-) isomer exhibits both these desired characteristics of treating cardiovascular disorders and, at the same time, reducing undesirable side effects.

The present method provides a safe, highly effective method for treating cardiac disorders associated with angina pectoris and/or hypertension.

Detailed Description of the Invention

The present invention relies on the beta-blocking activity of the levorotatory enantiomer of nadolol, referred to as S(-) nadolol, to provide enhanced beta-blocking activity (for example, as treatment for angina pectoris or hypertension) without many of the undesirable side effects associated with beta-blockers.

The particular side effects which may be reduced or eliminated by the present invention may include any one or a combination of the following, depending on the particular response of an individual to the drug: (a) cardiovascular effects such as excessive bradycardia, impaired peripheral vascular circulation (for example typified by symptoms of the Raynaud type), cardiac rhythm/conduction disturbances and/or atrioventricular block; (b) central nervous system effects, such as dizziness, fatigue, paresthesias, sedation and behavioral changes; (c) respiratory effects, such as bronchospasm; (d) gastrointestinal effects, such as nausea, diarrhea, constipation, and indigestion; (e) miscellaneous effects, such as impotence or decreased libido, headache, dry mouth, eyes or skin, and tinnitis, and dermatological

effects, such as causing or aggravating certain forms of psoriasis or exanthema.

In the present method, S(-)nadolol, which is substantially free of its R(+) enantiomer, is administered alone, or in combination with other drugs in adjunctive treatment, to an individual suffering from a cardiovascular disorder, such as heart disease, angina or hypertension. "S(-) nadolol" as used herein refers to the levorotatory isomer of cis-5-[3-[(1,1-dimethylethyl)amino]-2-hydroxypropoxy]-1,2,3,4-tetrahydro-2,3-naphthalenediol. The term "substantially free of the R(+) enantiomer" as used herein means that the composition contains at least 90% by weight S(-) nadolol and 10% by weight or less of R(+) nadolol. Preferably, the composition contains at least 98% by weight of S(-) nadolol and 2% or less of R(+) nadolol.

Racemic nadolol (i.e., a mixture of R(+) and S(-) enantiomers) has nonselective beta adrenoreceptor blocking activity. The S(-)isomer has the desired antihypertensive and antianginal activities. However, R(+) nadolol can induce significant side effects in some individuals. Thus, it is desirable to use the essentially pure S(-) isomer in cardiovascular applications, because it is much more cardioactive than the R(+) isomer, and because it minimizes the extra-cardiac activity associated with the undesirable side effects of the R(+) isomer.

In the present method, S(-) nadolol is administered to an individual suffering from a cardiovascular disorder, such as angina pectoris or hypertension. For

example, S(-) nadolol is administered therapeutically to an individual to reduce or ameliorate hypertension or to reduce the symptoms of angina pectoris. Alternatively, S(-) nadolol can be administered prophylactically to reduce the probability of occurrence of a heart attack or therapeutically after the occurrence of a heart attack.

The present method also has the advantage that it offers improved antihypertensive and antianginal therapy to patients with impaired renal function. Since nadolol is excreted mainly by the kidneys, it tends to accumulate to an undesired extent in cases of renal failure, leading to an aggravation of any one or several of the above-mentioned side effects. The presence of the undesired R(+) enantiomer of nadolol also places an unneeded burden on the kidney function of the patient since it must be excreted even though it contributes no desirable effect to the patient's benefit.

The present method also provides the unexpected benefit of reducing cardiac depressant effects of nadolol. Even though nadolol is known to possess lower myocardial depressant activity than propanolol, this characteristic is further reduced by use of the S(-) enantiomer in place of the racemic mixture. In some patients bradycardia (slowing of the heartbeat) and negative inotropic effects (weakening of the force of the heartbeat) can represent serious side effects and can lead to an increased risk of congestive heart failure or aggravation of an existing malady of this type. In the present invention, it is found that although R(+) nadolol is not useful in treating hypertension or angina pectoris, for example, it does contribute to the cardiac

depressant effects of the drug. Administration of S(-) nadolol essentially free of the contaminating R(+) enantiomer provides a significant reduction in the incidence or seriousness of such side effects.

The drug can be administered orally, by subcutaneous or other injection, intravenously, topically, parenterally, transdermally, rectally or via sustained release methods, e.g., an implanted reservoir containing S(-) nadolol. The form in which the drug will be administered (e.g., powder, tablet, capsule, solution, emulsion) will depend on the route by which it is administered. The quantity of the drug to be administered will be determined on an individual basis, and will be based at least in part on consideration of the individual's size, the severity of the symptoms to be treated and the result sought. In general, quantities of S(-) nadolol sufficient to reduce hypertension or reduce the symptoms of angina pectoris will be administered. For example, less than about 80 mg per day of S(-) nadolol (given in one dose or multiple doses) is usually sufficient to produce the desired effect. Some patients having hypertension, however, may require up to about 200 mg per day. Typically, a dose of about 20 to about 80 mg of S(-) nadolol per day will be administered.

In the method of the present invention, S(-) nadolol can be administered along with one or more other drugs. For example, other anti-hypertensive agents, such as bendroflumethazide or other thiazide-type diuretics, hydralazine, prazosin, and alpha-methyl dopa, can be given with or in close temporal proximity to administration of S(-) nadolol.

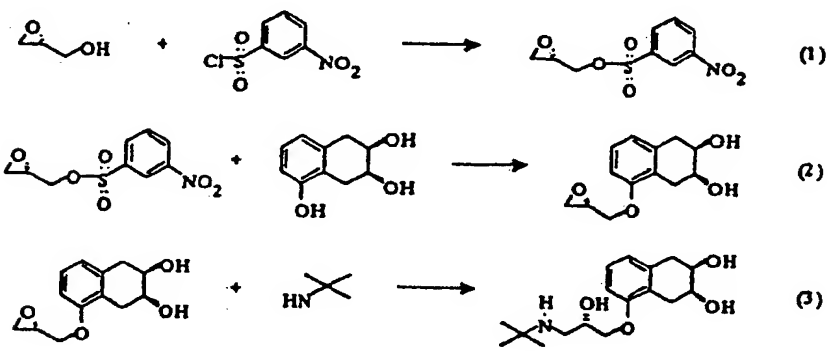
The two (or more) drugs (S(-) nadolol and another drug) can be administered in one composition or as two separate entities. For example, they can be administered in a single capsule, tablet, powder, liquid, etc. or as individual compounds. The components included in a particular composition, in addition to S(-) nadolol and another drug or drugs, are determined primarily by the manner in which the composition is to be administered. For example, a composition to be administered orally in tablet form can include, in addition to the drugs, a filler (e.g., lactose), a binder (e.g., carboxymethyl cellulose, gum arabic, gelatin), an adjuvant, a flavoring agent, a coloring agent and a coating material (e.g., wax or a plasticizer). A composition to be administered in liquid form can include the combination of drugs and, optionally, an emulsifying agent, a flavoring agent and/or a coloring agent.

In general, according to the method of the present invention, S(-) nadolol, alone or in combination with (an)other drug(s), is administered to an individual periodically as necessary to reduce or ameliorate symptoms of the hypertension or angina pectoris being treated while reducing or avoiding undesirable side effects associated with beta-blockers, including cardiac, respiratory, central nervous system, gastro-intestinal, and allergic reactions. The length of time during which the drugs are administered and the dosage will depend on the disorder being treated, the type and severity of the symptoms, and the physical condition of the individual being treated.

The invention is further illustrated by the following example. This example is not intended to be limiting of the invention in any way.

EXAMPLE I

SYNTHESIS OF S(-) NADOLOL



Preparation of S-Glycidyl m-Nitrobenzenesulfonate (reaction 1):

A solution of R-glycidol and triethylamine in toluene was cooled with ice water (ca. 5°C). m-Nitrobenzenesulfonyl chloride was added in portions while maintaining the temperature below 10°C. During the addition, a white precipitate (triethylamine hydrochloride) was formed. The mixture was stirred at room temperature for 22 hours. The mixture was then diluted with a small volume of ethyl acetate and

CLAIMS

1. Use of S(-) nadolol for the manufacture of a medicament for treating a cardiovascular disorder in an individual and reducing undesirable side effects associated with beta-blocking drugs, wherein the S(-) nadolol is in a therapeutically effective amount and is substantially free of R(+) nadolol.

2. The use of Claim 1 wherein the cardiovascular disorder is hypertension or angina pectoris.

3. The use of Claim 1 wherein the amount of S(-) nadolol in the composition is greater than about 90% by weight.

4. The use of Claim 3 wherein the amount of S(-) nadolol in the composition is greater than 98% by weight.

5. The use of Claim 1 wherein the amount of S(-) nadolol is an amount sufficient to reduce, ameliorate or eliminate the symptoms of the cardiovascular disorder and reduce or eliminate the undesirable side effects associated with the administration of beta-blocking drugs.

6. The use of Claim 5 wherein the undesirable side effects are related to cardiac depression.

7. The use of Claim 1 wherein the amount of S(-) nadolol is from about 20 mg to about 200 mg per day.

8. Use of S(-) nadolol and at least one other drug for the manufacture of a medicament for treating a cardiovascular disorder in an individual and reducing undesirable side effects associated with beta-blocking drugs, wherein the S(-) nadolol is in a therapeutically effective amount.

9. The use of Claim 8 wherein the other drug is an anti-hypertensive agent.

10. The use of Claim 9 wherein the anti-hypertensive agent is a thiazide-type diuretic, hydralazine, prazosin or alpha-methyldopa.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 92/05429

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 A 61 K 31/135

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl.5	A 61 K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No.[13]
X	GB,A,1464950 (E.R. SQUIBB AND SONS INC.) 16 February 1977, see whole document, especially page 1, lines 7-26 ---	1-7
A	EP,A,0105996 (MERCK AND CO. INC.) 25 April 1984, see page 2, line 11 - page 3, line 31; page 5, lines 12-31 ---	1-7
A	EP,A,0165450 (BAYER AG) 27 December 1985, see page 1, lines 1-5; page 3, lines 25-28 --- -/-	8-10

° Special categories of cited documents : [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
22-10-1992	20. 11. 92
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	

Form PCT/ISA/210 (second sheet) (January 1985)

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
A	Journal of Chromatography, vol. 539, no. 1, 8 February 1991, Elsevier Science Publishers B.V., (Amsterdam, NL), C.R. LEE et al.: "Liquid and high-pressure carbon dioxide chromatography of beta-blockers", pages 55-69, see abstract and introduction, pages 55-56, line 9	1-10

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. US 9205429 SA 62036

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 06/11/92
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Patent document cited in search report	Publication date	Patent family member(s)		Publication date
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		CA-A-	1064965	23-10-79
		CA-A-	1059147	24-07-79
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EP-A- 0105996	25-04-84	None		
EP-A- 0165450	27-12-85	DE-A-	3419130	28-11-85
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		JP-A-	60255724	17-12-85

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